The tumour should be at the centre of the excised sector. The integration of remodelling procedures is indicated for tumours located in the lower quadrants in order to obtain a safe oncological excision avoiding an insufficient cosmetic outcome. The pathologist must have all the necessary information about clinical and mammographics findings and the exact site of the lesion in the breast. The intact specimen with suture markers should be submitted to the pathologist. Every phase of the surgical procedure must be accurately recorded for favour quality control.

28 INVITED

Impact of adjuvant treatment on local control

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Treatment of operable breast cancer has greatly evolved during the last three decades. The updated 2000 overview on systemic adjuvant therapy has confirmed that, overall, some years of tamoxifen in estrogen receptor positive tumors and/or some months of polychemotherapy have both substantially decreased the risk of disease-relapse and improved total survival in groups of patients. On the other hand, breast conserving therapy, consisting of a wide surgical excision and postoperative breast irradiation, has replaced mastectomy for many primary breast cancers without adversely affecting total survival. Local control remains a crucial point in the management of breast cancer. Both randomized and observational studies have reported that adjuvant systemic therapy can greatly reduce the risk of local recurrence after breast-conserving approaches. By contrast, the role of postmastectomy irradiation (i.e. irradiation delivered to the chest wall, internal mammary nodes and ipsilateral supraclavicular nodes) is still debatable. A few randomized studies published in the late 1990s have reported that women who received both modalities had a significant reduction in the risk of locoregional failure, distant metastases and death compared to patients given adjuvant chemotherapy alone. It must be stressed, however, that the risk of locoregional relapses was very high (25–32% at 10 years) in this subgroup and that the chemotherapy regimen was delivered with suboptimal duration and intensity. Both radiotherapy and systemic therapy are not devoid of potential toxicities that can reverse favorable effects. Therefore, there is need to identify through properly designed prospective studies patients who are at high risk of local failure after optimal locoregional treatment and the absolute benefit they can achieve by a correct sequence of administration of both modalities to definitely improve both local and distant disease control.

29 INVITED

Long term effects of radiotherapy for breast cancer

E. Van Limbergen. *Department of Radiation Oncology - University Hospital Gasthuisberg - 3000 Leuven, Belgium*

Radiotherapy is increasingly used in the treatment of breast cancer. Randomised trials have consistenly established that survival rates after breast conserving surgery and radiotherapy are equivalent to those observed after modified radical mastectomy. Moreover during the same period of screening mammography has led to an increase in small tumours, ideally suitable for breast conservation. As a consequence, the use of breast conserving surgery and radiotherapy rose progressively the last 20 years.

The techniques of breast irradiation, matching techniques for locoregional treatment and boost deliver significant high doses to those patients.

Most of the data on long term effects such as cardiac toxicity, ribnecroses, lungtoxicity, comes from the earlier experience on adjuvant RT after MEC, but increasingly data becomes available on long term cosmetic damage, and complications after BCT.

Tangential RT does not contribute significantly to arm or shoulder symptoms after axillary disfection. Breast RT has a relatively minor influence on the long-term cosmetic result, which is a direct consequence of surgery. Boost doses and field matching overlap may lead to late skin necroses in high dose area. Cosmetic disturbing breast asymmetry and skin teleangiectases occur in 15–25% of patients.

Serious long-term complications, mostly anecdotal have only rarely been attributed to tangential breast RT.

Controlateral breast cancers and other second malignancies might be expected to become frequent in irradiated patients, no significant increase has been observed after local breast irradiation. The incidence of acute leukaemia seems increased in patients receiving chemotherapy in addition to breast irradiation.

Unlike tangential BRT, RT involving lymph nodal areas can course serious toxicity including arm lymph edema, brachial plexopolly, shoulder stiffness, and symptomatic lung reactions.

Although RT of the left breast sometimes encomposes a portion of the left ventricle no increase in cardiac morbidity or mortality has been associated with tangential fields only without lymph node RT. Data from the Stockholm trial suggests that excess cardiac mortality reflect the volume of heart irradiated to high dose. It has been hypothesised that irradiation of the great vessels might be an additional cause of vascular morbidity but clinical data are currently lacking. Moreover in trials started after 1975 no significant excess in node breast cancer mortality was observed after a median follow-up of 10 years. Although longer term confirmatory data is required from these newer studies, the weight of current evidence suggests that the marked increase in cardiovascular mortality found in patients irradiated using old techniques, is not likely to be observed with optimal contemporary RT practices.

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SYMPOSIUM

Impact of digital techniques in breast imaging

30 INVITED

Clinicial experience with FFDM

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The Princess Grace Hospital in London was the first breast unit in the UK to install FFDM (GE 2000D) in January 2000. To date there are only two such machines in the UK and the unit has carried out 8,000 examinations working alongside a conventional Siemens 3000 machine. Online CAD has been installed recently and experience is being gained with this.

Our conclusions for FFDM are as follows:

(1) Popular with patients and staff (survey results)
(2) Short learning curve
(3) Image quality scores from soft copy reporting clearly superior to those of hard copy.
(4) Hard copies do not do justice to image quality
(5) Soft copy reporting takes slightly longer but imparts greater confidence due to image manipulation.
(6) No significant problems comparing with previous analogue films.
(7) Microfocus magnification not usually necessary due to on screen magnification.
(8) Advantage of data display on all films.
(9) Multiple advantages from electronic archiving system.
(10) All four radiologists in the unit would purchase digital compared to analogue if given the choice.

The overall popularity and advantages of the system allied to future development potential offer an exciting prospect for the future of mammography. In addition the unit has proved an excellent charitable fund raising tool.

31 INVITED

Clinical experience in full field digital mammography II

G. de Geer, J.Ch. Piguet, F. Couson. *Clinique des Grangettes, Radiology department, Chene-Bougeries, Switzerland*

Our experience on FFD mammography is based on 35000 patients with 4 views each on a 50-60 cases a day basis over a period of approximately 30 months. We have been using computer-aided detection (CAD from R2 technology) for the last 12 months.

The system is used for diagnostic mammography and not for screening cases. Our local Swiss screening program does not yet accept the FFD system, preferring to maintain uniformity within the present screening program thereby also permitting small radiological centres to survive.

The mammography section of our department has been modified as follows:

– 1 mammography room with a General Electric FFD 2000 and a viewing console
– 3 examination rooms with ultrasound and interventional equipment
– 1 mammography room with a regular mammograph for the local screening program
– 1 reading room with view boxes, a reading console and CAD
– 1 stereotactic GE Senovision with Mammotome

The main mammography room is used only for making the exposure.

Since the technologist checks the image quality within a few seconds, a new exposure can immediately be done if necessary without loss of time.

During printing on a high-resolution laser film printer, the patient is accompanied to an examination room.

The radiologist, reads the films and CAD on the reading console, compares the pictures with the old films on a view box. He then examines the patient, does a breast ultrasound exam followed by cytology or micro biopsy when needed. The results and films are given to the patient and the report is sent to the referring physician.

Such a powerful tool as the FFD 2000 easily takes 7-8 diagnostic mammography /hour. Because of possible time limitations, the physical exam should not be done in the same room and we believe that interventional procedures should not be done on such a system even if technically feasible.

The CAD is known to detect around 20% more breast cancers than the radiologist alone. This great tool represents a progress as long as it is used before the physical exam. According to the CAD result, the diagnosis can then be improved by a tailored magnification view or an ultrasound exam.

32 INVITED

Application of mri to diagnosis and treatment of breast cancer

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MRI became clinically valuable for the detection and characterization of breast cancer after the introduction of Gd-DTPA contrast agent. Currently, contrast-enhanced (CE) MRI is capable of detecting mammographically occult cancers, even in dense breast tissue. It shows tumor extent in 3-D, employing magnetism rather than ionizing radiation. Nonetheless, CE MRI has two major drawbacks: its high cost and limited, varying specificity. As a consequence, application of CE MRI is often restricted to selected indications, e.g., suspicion of multifocal/multicentric disease, and detection of the unknown primary in patients with positive lymph nodes.

New applications of CE MRI in diagnosis and treatment of breast cancer are currently investigated. Worldwide multi-institutional trials assess the efficacy of MR screening in women at high lifetime risk of breast cancer. Preliminary results from our institute show high sensitivity but lower specificity for this population, resulting in frequent biopsies on benign lesions. A clinical workstation has been developed to offer objective and reproducible guidelines for the interpretation of MR screening images. In agreement with findings from other groups, combination of computer-rated washout of contrast, smoothness of uptake, mean and variation of margin sharpness yielded significant contribution to the characterization into benign and malignant lesions: estimated NPV exceeds 98% at 50% PPV. These results indicate capability of the system to reduce the number of biopsies on benign lesions in screening without compromising the ability to exclude malignant disease.

Application of CE MRI is currently also investigated for pre-operative estimation of tumor extent aimed at staging and treatment selection, as well as for guidance to breast-conserving surgery and post-operative boost irradiation. For this purpose, the geometrical reproducibility of the mammary gland structure between diagnostic imaging and treatment was estimated by quantification of tissue shifts in the breasts of healthy volunteers using repeat MR setups in supine orientation. Fiducial points in the mammary gland structure were identified and automatically registered with their counter locations in the repeat MRI scans. Margins (5 mm) were derived to take this geometrical uncertainty into account.

Future developments in MRI technology and contrast agents will provide new insights and advances in the diagnosis and treatment of breast cancer.

34 INVITED

Ultrasound: high-frequency, 3D and contrast agents

G. Rizzatto. *Vittorio Emanuele III Hospital, Department of Diagnostic Imaging, Gorizia, Italy*

The diagnostic role of breast ultrasound (US) has been expanded along with the improvement of high frequency transducers and digital technology. Vascular assessment has progressed enough to depict normal vascular anatomy of the breast and the lymph nodes. Pathologic vessels are seen in almost all the tumors, thus improving US sensitivity for nonpalpable carcinomas. New contrast agents will recirculate enough to search for vascular foci during a thorough investigation of both breasts and nodal stations.

US role in screening might be now revised. Many factors are now in favour of targeted US screening in dense and complex breasts, and in high risk patients. Screening sensitivity is significantly increased; most of these US detected tumors are small enough to be curable. Mammography and sonography together are an unique problem solving, and cost effective tool. They can easily guide fine aspirations or larger biopsies reducing the cost of unnecessary surgical procedures.

Accurate US investigations facilitate the surgical approach to a very conservative and cosmetic operation. High-resolution sonography can demonstrate the intraductal spread of tumors and their multiple foci more easily than mammography; but US diagnosis is less sensitive than magnetic resonance mammography in the evaluation of the real tumoral extent. Ductal branching has a complex pattern; therefore intraductal spread and multifocal nodes are better demonstrated by multiplanar analysis of 3D ultrasound data volumes. Sonography can easily explorate the different nodal chains. Metastatic disease is indicated by an enlarged and round shape and the absence of the echogenic hilum. Irregularities in the cortex are a very useful sign in metastatic nodes without total replacement of lymphoid tissue by neoplastic cells. These signs are very specific. A time consuming, radiation emitting and costly sentinel biopsy may be avoided in one every five clinically node-negative patients. But preoperative US assessment is also important as sonography is very sensitive in patients with extensive nodal involvement that might result negative at the sentinel node procedure. New technologies and contrast agents allow perfusional studies that enhance the contrast resolution and will increase the sensitivity of US for small nodal metastases.

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SYMPOSIUM

Pathology: the interface molecular – histopathology

35 INVITED

Molecular changes in normal breast epithelial cells and 'borderline' epithelial proliferations - implications for classification of breast disease

S.R. Lakhani. *Institute of Cancer Research, The Breakthrough Toby Robins Breast Cancer Researc, London, United Kingdom*

Breast cancer is thought to arise in a multistep fashion. A transition from normal epithelium to invasive carcinoma via non-atypical and atypical hyperplasia and in situ carcinoma has been proposed. The introduction of mammographic screening has led to the increased detection of 'borderline lesions' and this has highlighted deficiencies in our understanding and classification of breast disease. Atypical Ductal Hyperplasia (ADH) is a controversial lesion, which shares features with DCIS and non-atypical hyperplasia. Despite clear diagnostic criteria agreement even amongst experienced breast pathologists has been low. Molecular analysis using LOH and CGH has demonstrated genetic changes with similar frequency to that seen in DCIS and invasive cancer. This indicates that ADH is a clonal (neoplastic) proliferation and raises questions about the validity of separating ADH from DCIS as a separate entity.

Retrospective studies indicate that Hyperplasia of Usual Type (HUT) has a relative risk of 2 for the subsequent development of invasive carcinoma. LOH at many different loci have been identified in HUT with frequencies ranging from 0-15%. These frequencies are lower than in DCIS and ADH (range 25-55%). At least a proportion of non-atypical hyperplasia is therefore also clonal, neoplastic proliferation and is likely to be non-obligate precursor. Should the proliferative lesions be classified using -intraepithelial neoplasia- classification similar to CIN in the cervix?

Apocrine papillary hyperplasia is considered to be a benign lesion despite a similar architecture to low grade DCIS. Our laboratory has investigated genetic alterations in benign apocrine hyperplasia and compared these to apocrine ductal carcinoma in-situ (DCIS) and invasive apocrine carcinomas of the breast using CGH. All lesions exhibited DNA copy number changes. The average number of alterations in apocrine hyperplasia was 4.1 compared to 10.2 in apocrine DCIS and 14.8 in invasive carcinoma. The changes show considerable overlap with those identified in in-